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Tumor recurrence patterns in eloquent glioma after microsurgical resection and adjuvant radiochemotherapy

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Abstract

Background. Evidence on the influence of eloquent brain areas on the effectiveness and side effects of radiotherapy (RT) remains limited. This study evaluated the relationship between eloquent brain regions, radiation dose, and tumor recurrence patterns in glioma patients.

Methods. Preoperative navigated transcranial magnetic stimulation (nTMS) mapping of language and motor function, complemented by nTMS-based tractography, was performed. Magnetic resonance imaging of tumor recurrence was co-registered with RT treatment plans and functional nTMS data. Tumor growth direction, radiation dose to eloquent structures, and clinical outcomes were analyzed.

Results. Seventy-two patients with glioblastoma, aged 57.7 ± 14.8 years, were included. Tumor recurrence toward eloquent brain areas, assessed either by volumetric or linear measurements, indicated growth affecting motor function in 68.1% and language function in 79.3% of patients. Following RT, new motor deficits occurred in 3/48 patients (6.3%) and language deterioration in 3/20 (15.0%). The mean dose to the corticospinal tract was 10.1 Gy in patients with motor decline versus 3.7 Gy in those without ($P = .137$). For language fiber tracts, corresponding doses were 34.1 Gy and 15.1 Gy ($P = .073$).

Conclusions. Tumor recurrence toward eloquent brain areas was observed, with high radiation doses to eloquent brain areas being associated with higher rates of neurological deterioration. These findings create an ambiguous situation regarding the application of high radiation doses to the resection cavity facing eloquent brain areas while simultaneously ensuring optimal dose gradients to spare those.

Key Points

- Recurrent glioblastomas frequently grow toward motor- and language-eloquent fiber tracts, highlighting the need for individualized surveillance and treatment strategies.
- Higher radiation doses to eloquent fiber tracts correlate with increased rates of neurological impairment, including motor and language deficits.
- Functionally guided radiotherapy planning using navigated transcranial magnetic stimulation (nTMS)-based mapping and fiber tracking may optimize tumor control while minimizing toxicity to eloquent brain areas.

Importance of the Study

This study demonstrates that recurrent glioblastomas exhibit a marked growth tendency toward motor- and language-eloquent fiber tracts. By integrating navigated transcranial magnetic stimulation (nTMS)-based functional mapping and tractography with radiotherapy (RT) planning data, we show that higher radiation doses to eloquent fiber tracts are associated with increased rates of motor and language deficits. This work provides a combined analysis of tumor recurrence directionality and radiation-induced toxicity using individualized, function-based imaging. Our findings highlight a clinical dilemma: while high RT doses near the resection cavity are necessary for tumor control, they may compromise neurological function if eloquent structures are involved. These results underscore the need for patient-specific, function-guided RT planning that balances oncological efficacy with preservation of quality of life. This approach may serve as a blueprint for future prospective trials and supports a paradigm shift toward incorporating functional data into standard glioblastoma treatment protocols.

Glioblastomas are highly malignant brain tumors. Even after microsurgical resection followed by adjuvant radiochemotherapy, 90% of glioblastomas (GBM) show recurrence within 2 years.[1] Therefore, estimating potential tumor spread and predicting sites of tumor recurrence might influence treatment strategies by taking these findings into account in radiotherapy treatment planning. Tumor spread can often be observed along preformed structures in the brain, such as white matter fiber tracts (FT) or vessels.[2] Eloquent brain areas might also impact the tumor recurrence pattern. Sollmann et al. observed a growth tendency toward the motor cortex in patients suffering from high-grade glioma undergoing surgery.[3]

On the other hand, intensified treatment of glioma in eloquent brain areas by radiotherapy (RT) bears a considerable risk of neurological impairments. Ma et al. observed a significant reduction in the mini-mental status examination at follow-up in patients with high RT dose compared to patients prescribed low-dose RT.[4] Higher brain functions, including memory, learning, speed of information processing, and attention, can be impaired by radiochemotherapy.[5] Apart from a neurocognitive decline, further neurological deficits, including motor, sensory, and visual deficits, as well as aphasia, were reported after cranial RT.[6,7] These findings warrant the need for patient-tailored approaches to spare eloquent brain areas in RT treatment planning to reduce RT toxicity.[8,9]

However, we still lack evidence regarding the optimal RT planning strategy for tumors near the eloquent brain. In these cases, we face an ambiguous situation between extending the planning and boosting volumes to reduce to risk of local recurrence and the increased risk of local toxicity.

The aim of this study was to assess the impact of eloquent brain areas and FT on tumor recurrence patterns, with consideration of the applied radiation dosage in regard to potential radiation-induced toxicity.

This study evaluated the effect of the spatial relationship between the tumor and the cortical and subcortical eloquent brain areas on tumor recurrence patterns as well as radiotherapy-induced toxicity in glioma patients.

Materials and Methods

Ethics

The local ethics board approved the study (registration number: 2022-267-S-KH). We performed the study in accordance with the Declaration of Helsinki and the STROBE statement. All patients included in this study provided written informed consent.

Study Protocol

Patient selection.—Patients between 2016 and 2020 were retrospectively included. The inclusion criteria in this study were histopathologically diagnosed GBM WHO CNS 4, eloquent tumor location, preoperative nTMS examination, subsequent primary microsurgical resection, and adjuvant RT at our institution with radiologically confirmed tumor recurrence.

Patient data.—Patient data, including IDH status, patient characteristics, functional and neurological status, histopathological findings, imaging data, and radiation treatment plans, were analyzed.

Navigated transcranial magnetic stimulation.—nTMS mapping of the cortical representation of motor and language function was preoperatively performed according to clinical routine (Nexstim NBS 4.3 and NBS 5, Nexstim Plc.). For motor mapping of the upper extremity muscle representations, an intensity of 110% of the resting motor threshold (rMT) was chosen, while for lower extremities, an intensity of at least 130% of the rMT was applied.[10] For language mapping, an object naming task during repetitive nTMS (5 Hz) with an intensity of 110% of the rMT was performed.[11]

nTMS-based fibertracking.—Motor- and language-eloquent subcortical brain areas were identified using nTMS-based fibertracking. T1-weighted magnetic

resonance imaging (MRI) with intravenous contrast administration (CA) and diffusion tensor imaging sequences with 32 orthogonal sequences were acquired preoperatively in all cases. Subsequently, distortion correction was performed using Brainlab Distortion Correction software (version 6.2, Brainlab AG). Fibertracking was performed using a standard deterministic algorithm, applying fiber assignment by continuous tracking (iPlanNet Cranial, version 3.0.1, and Brainlab Elements Fibertracking, version 2.0, Brainlab AG).[11–13] For fibertracking of motor-eloquent subcortical pathways, motor-eloquent brain areas, identified by nTMS, as well as the ipsilateral brain stem, were selected as regions of interest (ROIs).[14,15] For fibertracking of the language function, nTMS language-positive cortical sites were set as ROIs, and a minimum fiber length of 100 mm was applied.[14,15]

Data processing.—Preoperative MRI, including nTMS data and nTMS-based fibertracking, was elastically fused with postoperative MRI and MRI with recurrence using Brainlab Elements ImageFusion (version 4.0, Brainlab AG) software to correct for brain shift and inaccuracies. In all patients, the initial tumor, the resection cavity, and the recurrent tumor volumes were contoured in Brainlab Elements SmartBrush (version 3.0, Brainlab AG) using T1 + CA MRI sequences.

Analysis of tumor recurrence.—The growth direction of tumor recurrence was measured linearly and volumetrically using Elements Viewer 5.2 (version 5.2, Brainlab AG). For linear measurements, the shortest distances between the resection cavity and the nearest motor or language FT and between the tumor recurrence and the motor and language FT were measured in all 3 image planes (Figure 1). In case of postoperative residual tumor, the residual tumor edge, as well as the resection cavity, was taken for reference. If the distance between the recurrence and eloquent FT was smaller than the distance between the resection cavity or residual tumor and eloquent FT, a growth tendency toward eloquent FT was assumed. In addition, tumor volumes oriented toward motor- or language-eloquent FT were calculated (Figure 2). If the relative volume of the recurrence was at least 35% of the total recurrence volume, a growth tendency toward the eloquent FT was assumed. A relative volume fraction of 35% was set as a limit value before the evaluation, based on the volumetric consideration that just over a third of the total volume grows in the direction of eloquent FT. The reference point for the volumetric growth assessment was the center of the recurrence.

Neurological status.—The neurological status, including the motor and language status, was analyzed preoperatively, postoperatively, before RT, after RT, and at 6-month follow-up. Motor function was categorized according to the British Medical Research Council (BMRC) grading, whereas the language status was evaluated using a modified Aachen Aphasia Test (AAT) classification.[16,17]

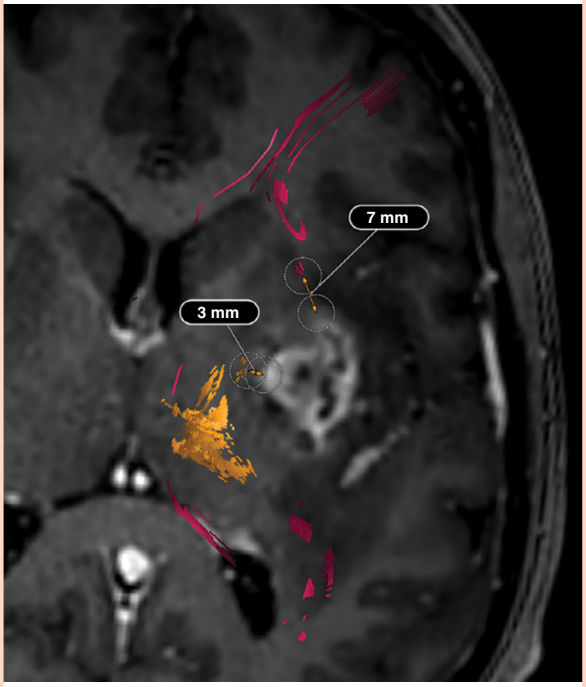

Figure 1. Linear measurement of distance between recurrence and eloquent fiber tracts. This figure displays the distance in mm between recurrence and eloquent fiber tracts (FT) on the left hemisphere. The corticospinal tract (CST) is displayed with a minimum distance of 3mm to the lesion and language FT with a minium distance of 7mm. The imaging modality used was an MRI T1 contrast enhanced in the axial plain. The image was created using Brainlab Elements Viewer (version 5.2, Brainlab AG).

Analysis of radiotherapy treatment plans.—Radiotherapy plans were calculated for a dose prescription of 30 × 2 Gy based on computed tomography (CT) imaging according to the guidelines of the European Society for Radiotherapy and Oncology on target delineation and radiotherapy details for glioblastoma in the patients included in this study.[9]

To merge the data of the CT-based RT plans with MRI data including functional data, the RT planning objects, including the relative isodose levels 105%, 100%, 95%, 90%, 80%, 60%, 40% and 20% of the prescribed dose, the gross tumor volume and the planning tumor volume were converted into digital imaging and communications in medicine (DICOM) structures, using the RT planning software Eclipse (version 16.0, Varian Medical Systems). For patients with sequential boost dose concepts, all isodose objects were created for the main plan and the boost plan, and combined.

The isodose level covering at least 70% of the FT was used as the radiation dose to the eloquent FT. In addition, the volume of the FT receiving at least 90% of the total dose was analyzed. For all isodose levels, the overlapping volumes with the motor and language FT were measured using Brainlab Elements Contouring (version 4.0, Brainlab AG). The radiation doses applied to eloquent brain structures were correlated with the occurrence of new

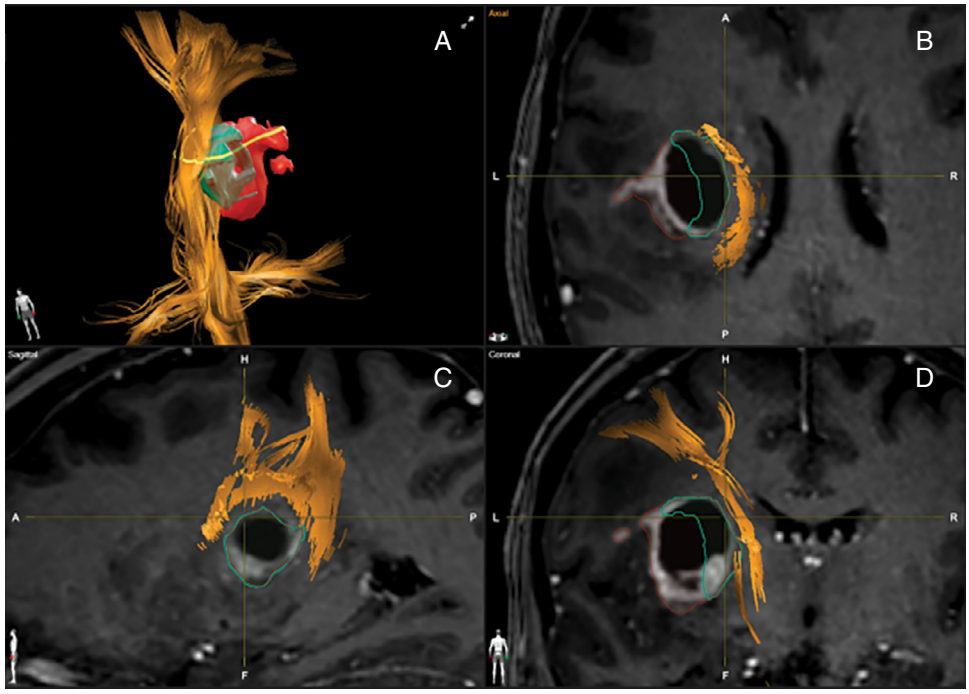

Figure 2. Volumetric measurement of the portion of recurrence toward the corticospinal tract. This figure displays the volume of the tumor recurrence (green) in relation to the corticospinal tract (CST) (orange). The recurrence is pictured in red (A) and the CST in orange. Picture A shows the three-dimensional volume pointing toward the CST in green. The other 3 pictures display the volume toward the CST two-dimensionally in the axial (B), sagittal (C) and coronal (D) plain. The image was created using Brainlab Elements SmartBrush (version 3.0, Brainlab AG).

neurological impairments during RT. Subsequently, patients with and without new neurological deficits after RT were compared.

Statistical Analysis

Statistical analyses and the creation of graphs were conducted using Prism (version 10.0.2; GraphPad Software). Descriptive statistics were applied for patient- and tumor-related characteristics as well as for RT doses and volumes analyzed in the present analysis. Tests for statistical significance between values were performed using Wilcoxon signed-rank tests and *t*-tests for paired samples. Testing was performed with a level of statistical significance set at $P < .05$.

Results

Patient Cohort

Seventy-two patients aged 57.7 ± 14.8 (range: 11–85) years at the time of RT were included in this study (Table 1). nTMS motor mapping was performed in 69 (95.8%) patients (26 with motor and language FT and 43 with only motor FT), and language mapping in 29 (40.3%) patients (26 with motor and language FT and 3 patients with only language FT). Postoperatively, residual contrast-enhancing tumor volumes were observed in 39 of the 72 patients (54.17%) after resection.

Growth Tendency Toward Motor Function

The mean volume of the tumor recurrence was 11.2 ± 21.6 cm^3 (range: 0.1–132.8). Regarding linear measurements, the recurrent tumor was closer to motor-eloquent brain structures in 30 cases (43.5%). In 4 of the 69 patients (5.8%), the distance was equal, and in 35 of the 69 patients (50.7%), the distance between the recurrence and eloquent FT was higher than the distance between the resection cavity and eloquent FT. The mean difference between the distance measured from the resection cavity to FT and the recurrence to FT was –2.4 ± 12.7 mm (range: –47.0 to 35.0, $P = .311$).

In 32 patients (46.4%), a volumetric growth tendency toward the CST was observed, while in 37 patients (53.6%), the relative volume of eloquent FT was lower than 35%. The mean volume ratio toward motor-eloquent structures was 34.0% ± 16.9% (1.7%–75.4%).

In 15 of the 69 patients (21.7%), both linear and volumetric growths were simultaneously observed. In 47 of the 69 patients (68.1%), there was either a linear or a volumetric growth tendency toward motor-eloquent regions (Table 2).

Growth Tendency Toward Language Function

Twenty-nine patients with data on language function were assessed. In the linear measurement, the recurrence was located closer to the language FT than the resection cavity in 11 of the 29 patients (37.9%), whereas in

Table 1. Patient Characteristics

Age (Mean ± SD (Min–Max))	57.7 ± 14.8 (11.0–85.0) years
Gender (*n* (%))	
Male	49 (68,1%)
Female	23 (31.9%)
Fiber tract qualities available in patients (*n* (%))	26 (36.1%)
Motor and language FT	43 (59.7%)
Only motor FT	3 (4.2%)
Only language FT	
Time to recurrence (Mean ± SD (Min–Max))	239.7 ± 211.2 (9.0–932.0) days
Tumor volume preoperatively (Mean ± SD (Min–Max))	30.5 ± 33.0 (0.1–161.3) cm^3
Residual tumor after surgery (*n* (%))	39 (54.2%)
IDH status of the tumor	
Mutated	13 (18.1%)
Wildtype	59 (81.9%)
Total radiotherapy dose (Mean ± SD (Min–Max))	56.8 ± 7.2 (34.0–60.0) Gy
Volume of tumor recurrence (Mean ± SD (Min–Max))	11.2 ± 21.7 (0.1–132.8) cm^3

Table 1 illustrates patient and tumor characteristics of all 72 patients. SD, standard deviation.

7 patients (24.1%), the recurrences showed an equal distance, and in 11 patients (37.9%), the recurrence was more distant. The mean difference between the 2 distances was –1.9 ± 13.4 mm (range: –55.0 to 26.0, $P = .553$).

A volumetric growth tendency toward the language FT was observed in 20 out of 29 patients (69.0%). In 9 of 29 patients (31.0%), the relative volume toward FT was lower than 35%. The mean volume ratio toward language FT was 37.4% ± 18.4% (3.5%–63.6%).

In 8 of the 29 patients (27.6%), both linear and volumetric growths were simultaneously observed. In 23 of the 29 patients (79.3%), there was either a linear or a volumetric growth tendency toward language-eloquent FT (Table 2).

Effect of RT on the Patient Outcome

Motor evaluation was performed in 48 patients. Three of 48 patients (6.3%) deteriorated in muscle strength after RT, whereas in 32 of the patients (66.7%), motor function remained unchanged or improved in 13 patients (27.1%). On average, muscle strength improved during RT. The median BMRC strength grade before and after RT was 5 (0–5).

Twenty patients had records regarding language function before and after RT. Three of 20 patients (15.0%) showed a worsening in language function after RT determined by the modified AAT, whereas in 13 of the patients (65.0%), the language performance was unchanged, and improved in 4 patients (20%). On average, the AAT before and after RT remained unchanged.

Effect of postoperative RT on motor function.—Motor status was available for 48 patients. The median BMRC strength grade before and after RT was 5 (0–5). Three of the 48 patients (6.3%) experienced a deterioration in muscle strength after RT. Thirty-two of the patients (66.7%) showed unchanged motor function, while 13 patients (27.1%) improved (Table 3). Among patients with new motor deficits, the mean volume of the motor-eloquent structures irradiated with at least 90% of the total radiation dose was 20.7 ± 6.9 cm^3 (range: 13.9–27.7 cm^3). In contrast, it was 11.3 ± 7.9 cm^3 (range: 0–26.5, $P = .049$) in patients without deficits (Figure 3, right panel). The mean radiation dose for 3 patients (6.3%) with motor deficits was 10.1 ± 9.3 Gy (range: 0–18.4 Gy), compared to 3.7 ± 7.1 Gy (range: 0–24.0, $P = 0.137$) in patients without motor deficits (Figure 3, left panel).

Effect of postoperative RT on language fiber tracts and language function.—Twenty patients with data on language function and radiation dose of language FT were assessed.

Three of 20 patients (15.0%) showed a worsening in language function after RT, as determined by the modified AAT. Language performance remained unchanged in 13 patients (65.0%), whereas it improved in 4 patients (20%). On average, the AAT scores before and after RT remained unchanged. In patients who experienced a deterioration in language function after RT, the mean volume of language FT receiving at least 90% of the total radiation dose was 29.3 cm^3 ± 7.9 cm^3 (range: 20.5–35.6 cm^3), compared to 18.3 cm^3 ± 21.0 cm^3 (range: 3.5–46.0 cm^3, $P = .144$, Figure 4, right panel) in patients without deficits. The mean radiation dose to the language FT in patients with deficits was 34.1 Gy ± 22.5 Gy (range: 12.0–57.0 Gy), compared to 15.1 Gy ± 14.8 Gy (range: 0–48.0 Gy) in patients without deficits ($P = 0.073$) (Figure 4, left panel).

Discussion

In this study, nTMS-based mapping of cortical eloquent brain areas and function-based fiber tracking to accurately identify eloquent FTs was performed and assessed in the context of tumor recurrence patterns and radiation doses. Our study indicates that recurrent gliomas tend to grow moderately toward language and motor-eloquent FTs. In addition, we observed increased rates of neurological deterioration with higher radiation doses applied to eloquent brain areas.

Tumor Recurrence Patterns Toward Eloquent Fiber Tracts

In this study, we observed a growth tendency toward motor-eloquent lesions in either volumetric or linear measurements in 68.1% of cases, whereas for language function, a rate of 79.3% was observed. In addition, patients with neurological deterioration during radiotherapy showed considerable, yet not significantly higher radiation doses to eloquent brain areas.

Table 2. Summary Growth Toward Eloquent Fiber Tracts

	Motor	Language
Number of patients, *n*(%)	69 (100%)	29 (100%)
Linear growth toward FT (A), *n*(%)	30 (43.5%)	11 (37.9%)
Volumetric growth toward FT (B), *n*(%)	32 (46.4%)	20 (69.0%)
A and/or B, *n*(%)	47 (68.1%)	23 (79.3%)
A and B, *n*(%)	15 (21.7%)	8 (27.6%)

Table 2 shows a summary of the growth tendencies of tumor recurrence. The results for fiber tracts (FT) of motor function in 69 cases and for language function in 29 cases are outlined.

Table 3. Comparison of Patients With and Without New Deficits After Radiotherapy

	Motor deficit after RT	No motor deficit after RT	Language deficit after RT	No language deficit after RT
Number of patients (*n*(%))	3 (6.3%)	45 (93.8%)	3 (15.0%)	17 (85.0%)
Volume FT with at least 90% of total irradiation dose (Mean ± SD (Min–Max))	20.7 ± 6.9 (13.9–27.7) cm^3	11.3 ± 7.9 (0.0–26.5) cm^3	29.3 ± 7.9 (20.5–35.6) cm^3	18.3 ± 12.0 (3.5–46.0) cm^3
Absolute irradiation dose of FT (Mean ± SD (Min–Max))	10.1 ± 9.3 (0.0–18.4) Gy	3.7 ± 7.1 (0.0–24.0) Gy	34.1 ± 22.5 (12.0–47.0) Gy	15.1 ± 14.8 (0.0–48.0) Gy
Growth toward FT (Mean ± SD (Min–Max))	2.3 ± 14.2 (–14.0 to 12.0) mm	–1.9 ± 10.9 (–22.0 to 35.0) mm	–0.7 ± 12.0 (–13.0 to 11.0) mm	0.0 ± 9.4 (–13.0 to 26.0) mm
Volume of Recurrence toward FT (Mean ± SD (Min-Max))	37.4 ± 16.4 (23.7–55.6) %	34.4 ± 17.1 (1.7–75.4) %	43.1 ± 5.6 (36.8–47.7) %	40.7 ± 19.1 (3.4–63.6) %
Recurrence reached FT (*n*(%))	0 (0.0%)	6 (13.3%)	2 (66.7%)	6 (35.3%)
Distance FT to recurrence (Mean ± SD (Min–Max))	9.0 ± 7.8 (4.0–18.0) mm	16.1 ± 13.4 (0.0–42.0) mm	4.7 ± 8.1 (0.0–14.0) mm	8.9 ± 10.3 (0.0–36.0) mm
Deficit prior to RT (*n*(%))	1 (33.3%)	20 (44.4%)	3 (100.0%)	12 (70.1%)
Age at radiotherapy (Mean ± SD (Min–Max))	44.0 ± 23.0 (21.0–67.0) years	66.5 ± 13.5 (28.0–91.0) years	64.7 ± 10.7 (53.0–74.0) years	67.2 ± 10.4 (52.0–85.0) years
Time to recurrence (Mean ± SD (Min–Max))	399.0 ± 462.1(98.0–931.0) days	228.3 ± 197.6 (9.0–903.0) days	287.7 ± 314.1 (51.0–644.0) days	204.4 ± 185.3 (9.0–623.0) days
Preoperative tumor volume (Mean ± SD (Min–Max))	28.6 ± 18.7 (8.3–45.0) cm^3	27.0 ± 27.7 (0.1–112.9) cm^3	17.9 ± 15.0 (2.6–32.5) cm^3	21.5 ± 20.6 (0.2–68.1) cm^3
Residual tumor (*n* (%))	2 (66.7%)	24 (53.3%)	3 (100%)	6 (35.3%)

Table 3 compares the groups of patients with and without deficits after radiotherapy (RT). Fiber tracts (FT) were evaluated for 48 patients regarding motor outcomes and for 20 patients regarding language outcomes.

Sollmann et al. assessed the growth tendency toward motor-eloquent brain areas in glioma patients using nTMS and functional MRI.[3] The authors observed tumor growth toward eloquent brain areas in 69.0% of patients without residual tumor, in 64.3% of patients with subtotal resection and the tumor located in the resection cavity contralateral to the motor area, and in 66.7% of patients with residual tumor on the same side of the resection cavity regarding motor area.[3] Analyzing language FTs, it is important to note that the language network is more ubiquitously distributed across the hemisphere than CST, which consists of 1 large coherent fiber bundle. Consequently, a greater growth trend toward language FTs than the CST was observed. The hypothesis that glioma propagates along preformed structures has been posited for several years.[2,18] Supporting this, an MRI-based study by Esmaeili et al. involving repeated imaging in 56 GBM patients demonstrated that GBM proliferates along white matter tracts.[19]

Effect of Radiotherapy on Eloquent Fiber Tracts

These recurrence patterns in GBM characterized by a growth tendency and potential infiltration of eloquent FT underline the importance of assessing the effect of consecutive RT on those FT. Regarding radiation toxicity, various studies have already shown that RT can damage healthy brain tissue, resulting in both short-term and long-term neurological deficits.[4,6,20–23] In our study, 6.3% of patients experienced deterioration in motor function,

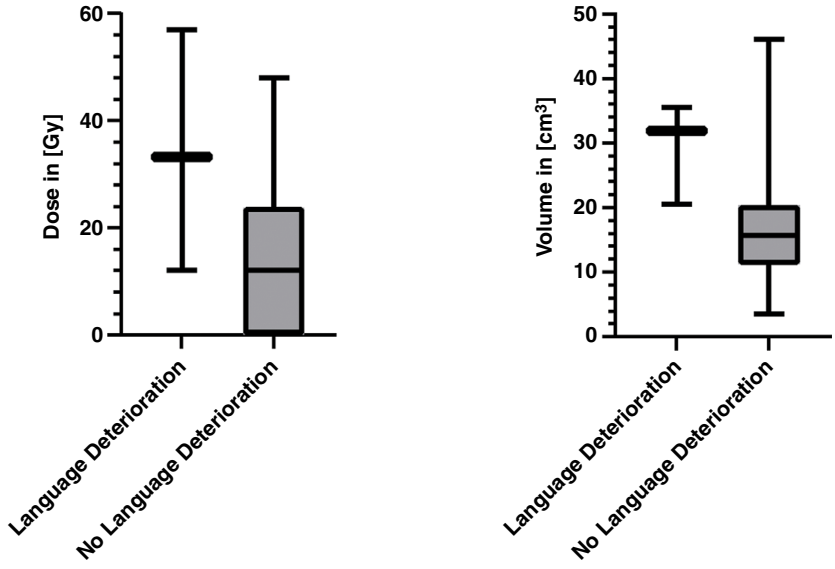

Figure 3. Absolute radiation dose and 90% isodose volume of motor-eloquent fiber tracts. This figure illustrates the absolute radiation dose in Gray (Gy), defined as the dose applied to 70% of corticospinal tract (CST) volume, for patients with and without motor deterioration. The right figure shows the absolute volume in cm^3 of the CST with at least 90% of the total radiation dose in patients with and without motor deterioration.

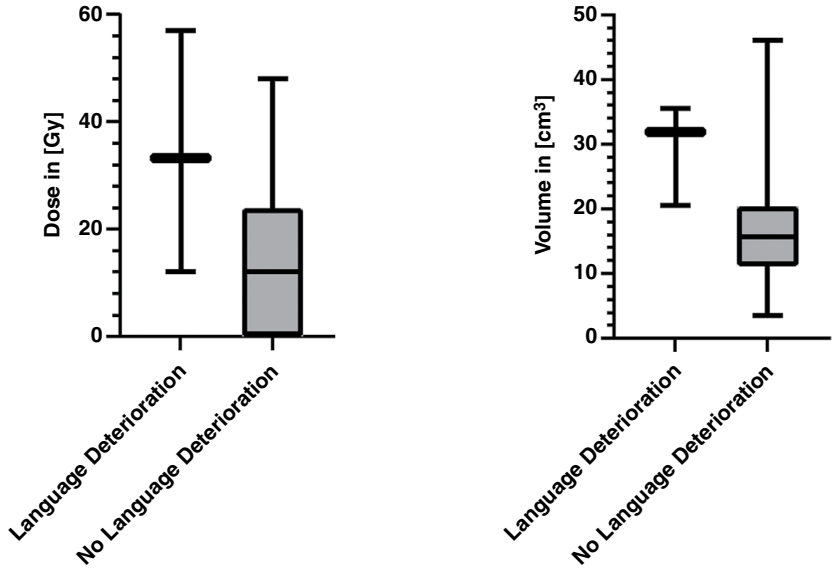

Figure 4. Absolute radiation dose and 90% isodose volume of language-eloquent fiber tracts. This figure illustrates the absolute radiation dose, defined as the dose applied to 70% of language fiber tracts volume, for patients with and without language deterioration. The right figure shows the absolute volume in cm^3 of the language FT with at least 90% of the total radiation dose in patients with and without motor deterioration.

and 15.0% of patients developed new language deficits after RT. Patients with radiotherapy-associated neurological deficits were found to have a larger volume portion of the eloquent FTs receiving at least 90% of the prescribed total dose. Additionally, the overall dose to eloquent FTs was higher in these patients. Comparing language and motor FTs, language FTs appear to be more sensitive to radiotherapy. A similar observation can be made when comparing the tumor-induced plasticity of the CST and language-eloquent FT.[24,25] Higher radiation doses correlated with increased occurrence rates of neurological deficits for both motor and language functions. In most of these patients, the resection cavity lies in close vicinity to eloquent FTs. Therefore, it remains uncertain whether these deficits were directly attributable to the effects of RT or were caused by the tumor itself, either through direct invasion into eloquent FTs or by secondary mechanisms, such as tumor-induced edema.

Implications on Function-Guided RT Planning

Reducing RT dose to healthy brain tissue can successfully be achieved on a cortical and subcortical level. Diehl et al. were able to significantly reduce the dose applied to the motor cortex without impairing tumor treatment volumes by optimizing volumetric modulated radiotherapy plans in 30 patients suffering from HGG.[10] Altabella et al. demonstrated in a study on 19 high-grade glioma patients that the radiation dose to language FT can be significantly reduced.[26]

In stereotactic radiosurgery, considering eloquent brain areas and FTs for radiotherapy planning can reduce the dose to those structures and subsequently lower the rates of neurological deficits.[27,28] Koga et al. found that implementing CST tractography led to motor impairments.[28]

Therefore, accurately delineating the region around the resection cavity, which may harbor residual tumor cells, and precisely identifying adjacent eloquent cortical and subcortical areas are crucial first steps in optimizing radiotherapy. In this study, we applied nTMS-based cortical mapping and function-based fiber tracking, which have already demonstrated high accuracy in identifying motor- and language-eloquent brain areas.[29] Dose concepts in eloquent glioma should be highly individualized to prioritize minimizing radiation exposure to eloquent brain areas outside the planning target volumes. Simultaneously, strategies for dose escalation or increasing planning target volumes around the resection cavity, such as simultaneous boost RT, should be considered to potentially target growth tendencies toward eloquent brain areas.[30] Achieving this requires a steep dose gradient in the specified region, which can be managed effectively using modern irradiation techniques.

Limitations

Because of the retrospective nature of this study, clinical examinations were limited to gross motor and language functions, and a small patient sample size prevents these findings from providing strong evidence to support exclusively pursuing one of the described treatment concepts. Therefore, we have to consider a treatment concept that addresses both the risk of tumor recurrence growth toward eloquent brain areas as well as potential radiation-induced toxicity by high radiation doses toward eloquent brain areas to address this tumor growth pattern.

Conclusion

Our study suggests that recurrent GBM tends to grow toward motor- and language-eloquent FTs. Furthermore, our findings indicate that high radiation doses applied to these tracts might lead to neurological impairments within a relatively short onset period. This presents a challenging dilemma: while high radiation doses are needed in the resection cavity, particularly toward eloquent brain areas, to address tumor spread, it is equally crucial to reduce the radiation exposure to these areas to prevent radiation-induced neurological deterioration. Further research is required to optimize radiotherapy planning, balancing the need for high radiation doses to control tumor spread with the imperative to minimize radiation-induced neurological deficits in eloquent brain areas, resulting in individualized RT planning.

Keywords

glioblastoma | radiotherapy | therapy-related deficits | functional imaging | tumor recurrence

Lay Summary

Gliomas are brain tumors that can return after treatment and may grow into areas that control important functions like movement and speech. The authors of this study wanted to understand how these important areas affect where the tumor grows back and whether radiation affects brain function. To do this, they used brain mapping tools before surgery in 72 people to locate regions linked to movement and language, then looked at where tumors returned and how much radiation those areas received. Their results showed that tumors often grew back toward these sensitive areas, and some people who received higher radiation doses to these regions experienced new problems with movement or speech.

Author Contributions

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Conflict of Interest Statement

S.M.K is a consultant for Brainlab AG, Ulrich Medical and Need Inc., shareholder of Need Inc., and received honoraria from Nexstim Plc, Spineart Deutschland GmbH, Medtronic AG, and

Carl Zeiss Meditec AG. B.M. received honoraria, consulting fees, research grants, and royalties from Medacta AG and Spineart Deutschland GmbH; honoraria, consulting fees, and research grants from Medtronic AG, Ulrich Medical GmbH, Brainlab AG, Icotec AG, and Carl-Zeiss, and honoraria and consulting fees from Companion Spine. B.M. received consulting fees, research grants, and stock options and holds an equity position in Sonovum GmbH. M.S. is a consultant for Level Ex Inc. and Sonovum GmbH. All authors declare no conflict of interest regarding the materials used or the results presented in this study. All authors declare no other relationships or activities that could appear to have influenced the submitted work.
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Ethics Statement

The local ethics board approved the study (registration number: 2022-267-S-KH). We performed the study in accordance with the Declaration of Helsinki and the STROBE statement. All patients included in this study provided written informed consent.

Data Availability

In the interest of patient privacy, all the collected raw data of individual cases is imparticipable. The anonymous datasets used and analyzed during the current study, the study protocol, and the statistical analysis plan are available upon reasonable request from the corresponding author to researchers who provide a methodologically sound proposal beginning 3 months and ending 5 years following article publication. Proposals should be directed to Maximilian.Schwendner@med.uni-heidelberg.de; to gain access, data requestors will need to sign a data access agreement.

Submission Statement

This manuscript is original and has not been submitted in part or whole elsewhere.

Previous Presentations

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